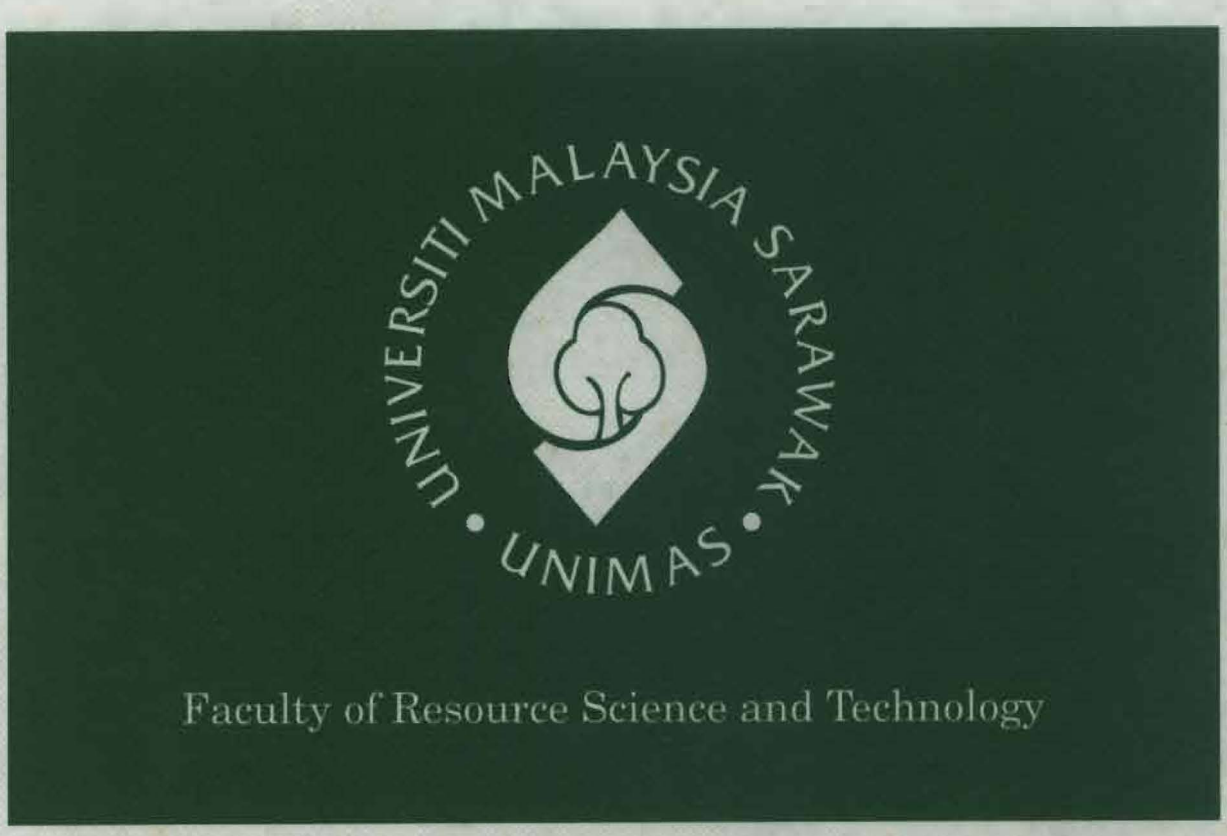

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDIES OF CHALCONES DERIVATIVES

Elissia Anak Agun @ Ensaring

Bachelor of Science with Honours
(Resource Chemistry)
2007

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDIES OF CHALCONES DERIVATIVES

ELISSIA ANAK AGUN @ ENSARING

This project is submitted in partial fulfillment of the requirements for the degree of

Bachelor of Science with Honours

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Faculty of Resource Science and Technology

UNIVERSITY MALAYSIA SARAWAK

2007

DECLARATION

No portion of the work referred to in this dissertation has been submitted in support of an application for another degree of qualification of this or any other university or institution of higher learning.

Elissia anak Agun @ Ensaring

Programme of Resource Chemistry

Faculty of Resource Science and Technology

University Malaysia Sarawak

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TABLE OF CONTENTS **Page**

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLE

Synthesis, characterization and biological activity studies of chalcones derivatives

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ABSTRACT

Two different pathways of etherification on chalcones' derivatives were studied. A series of alkyl halide consisting of C_3, C_4, C_5 carbon chain were introduced to the starting materials prior to the synthesis of chalcones' derivatives or *vice versa*. The yield obtained was calculated and the best pathway was suggested. All the etherified compounds were analyzed by FT-IR and CHN and tested for antibacterial activity against common *E. coli*. The preliminary antibacterial test showed that all compounds exhibited antibacterial activities to a certain extent against *E. coli*.

Keywords chalcone; antibacterial agent; in vitro

ABSTRAK

Terbitan bagi kalkon disintesis melalui dua tapakjalan yang berbeza. Siri alkyl halide yang mengandungi rantai karbon C_3, C_4, C_5 ditindakbalaskan dengan bahan pemula terlebih dahulu sebelum mensisntesis terbitan kalkon atau sebaliknya. Peratusan hasil dikira dan tapakjalan yang terbaik dikenalpasti. Semua terbitan kalkon dianalisis menggunakan FT-IR dan CHN. Seterusnya, terbitan tersebut diuji untuk aktiviti antibakteria terhadap E. coli. Ujian awal menunjukkan bahawa terbitan-terintan kalkon ini menunjukkan aktiviti yang positif terhadap E. coli.

Kata kunci : *kalkon ; agen antibacterial ; in vitro*

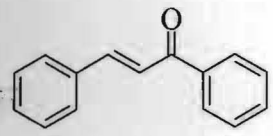
CHAPTER 1

Introduction

1.1 Chalcones and its derivatives

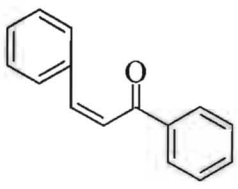
Chalcones are very common in natural product chemistry (Li *et al.*,2002). It is produced by plants as a pollinators' attractant, UV protector and insect repellents (Climent *et al.*,2004). Chalcones was reported to have biological properties and used widely especially as a medicine. For example, chalcones has shown antibacterial properties (Valla *et al.*, 2006), antitumoral, antihyperglycemic (Satyanarayana *et al.*,2004) , antifungal (Rao *et al.*,2004), antimalarial (Climent *et al.*,2004), antimicrobial (Valle *et al.*,2005), and antioedematogenic (Boeck *et al.*, 2006).

Chalcones is an α,ß-unsaturated ketones which consist of 2 aromatic rings joint together by 3-C skeleton. The other name for chalcone is 1,3-diphenyl-2-propen-1-one. Chalcones can be found in both *trans* **1** and *cis* **2** *formation* (Figure 1).



1

a) *Trans*



2

b) *Cis*

Figure 1: Chalcones in *trans* and *cis* form

Chalcones can be synthesized using Claisen-Schmidt condensation using benzaldehyde and acetophenone. This synthetic chalcones are important intermediates in the synthesis of many pharmaceuticals such as drug, sunscreen agent, photo resists and photographic emulsion (Valle *et al.*,2005).

Due to these important purposes, synthesis of chalcones and their derivatives have been carried out by many researchers to widen their usage. Some of those synthetic chalcones have shown similar activities as the naturally chalcones extracted from plants. Chalcones derivatives are very versatile as physiologically active compounds and substrates for the evaluation of various organic reactions (Yoshizawa and Shioiri, 2006).

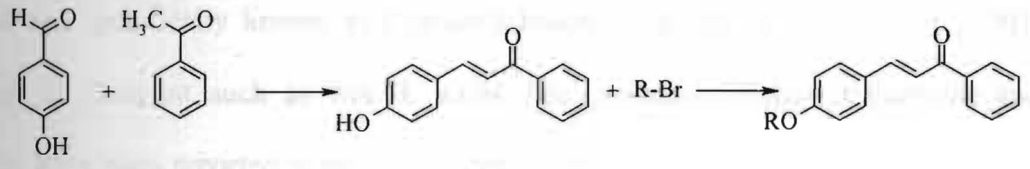
1.2 Objective

The main objectives of this research are:

a) To synthesis chalcones derivatives using two different strategies and compares the yield of the two strategies

i) Strategy 1

- Chalcones was synthesized using 4-hydroxybenzaldehyde and acetophenone, followed by etherification with a series of bromoalkane.

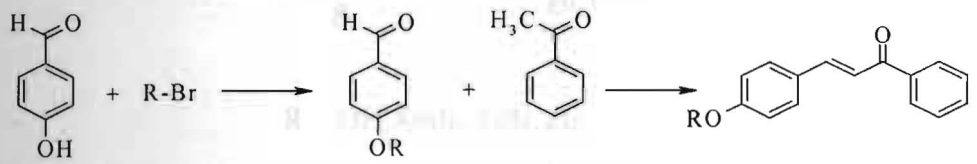


3 4 5 6

$R = C_3H_7, C_4H_9, C_5H_{11}$

ii) Strategy 2

- Etherification of 4-hydroxybenzaldehyde ring with series of bromoalkanes, followed by chalcones synthesis with acetophenone.



3 7 4 6

$R = C_3H_7, C_4H_9, C_5H_{11}$

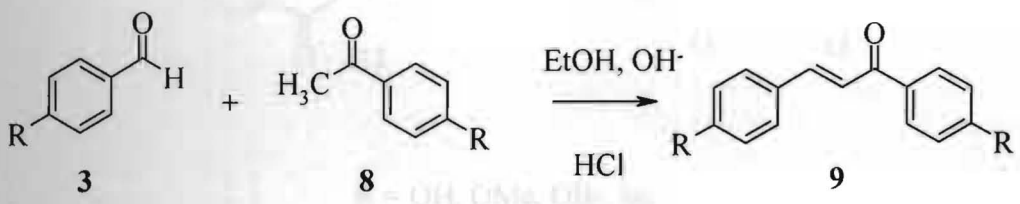
b) To perform bacteriostatic action on synthetic chalcones derivatives against *Escherichia coli*

CHAPTER 2

Literature Review

2.1 Chalcones Synthesis

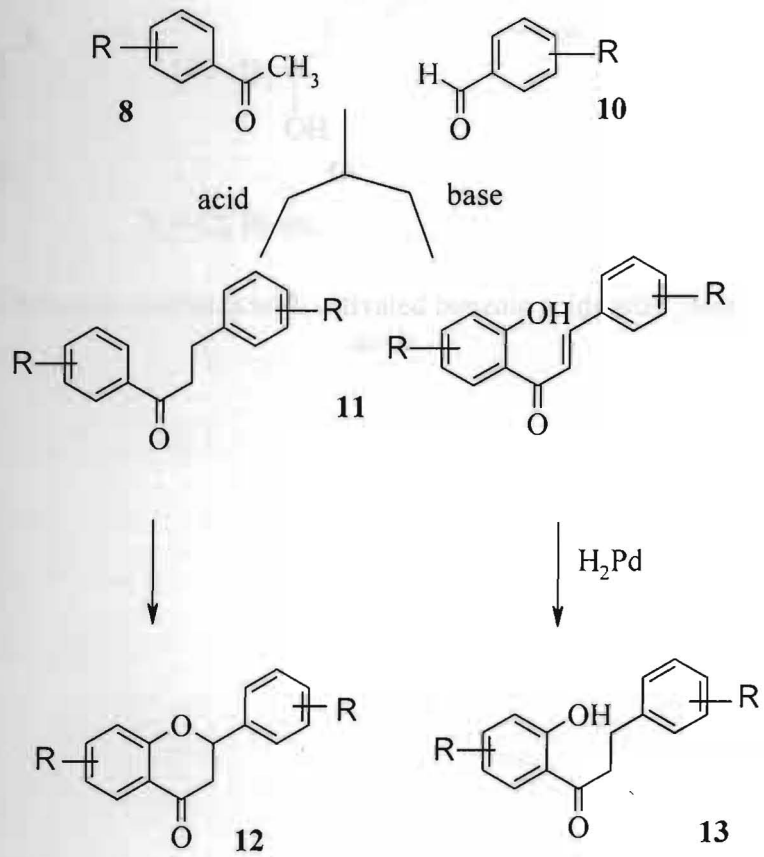
Chalcones can be synthesized using several methods. The very common method was by an aldol condensation between benzaldehyde and acetophenone in the presence of acids or bases as a catalyst under homogeneous conditions (Valle et al., 2005). This method was specifically known as Claisen-Schmidt condensation (Won *et al.*, 2005) (Scheme 1). Reagent such as NaOH, KOH, bis (*p*-methoxyphenyl) telluroxide and $Ba(OH)_2$ have been reported to be used to catalyst this condensation reaction (Li *et al.*, 2002).



R = OH, OMe, OBr, etc

Scheme 1 : Synthesis of chalcones by Claisen-Schmidt condensation

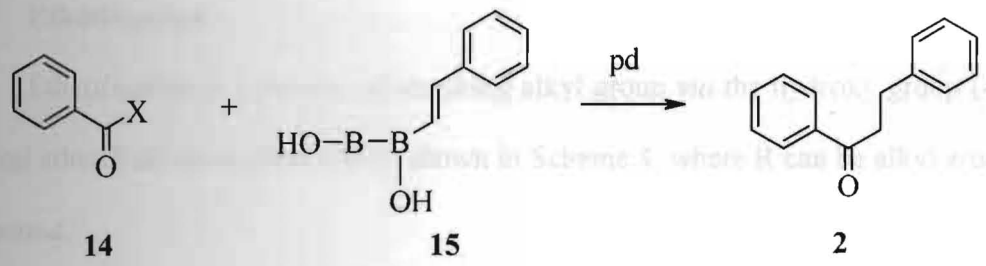
Chalcones and its derivatives can also be prepared by several methods such as base catalyzed aldol condensation or acid mediated aldolization (Marais *et al.*,2005). In Marais's research, aldol condensation is more feasible in basic condition. This is due to subsequent cyclization in acid condition which will to afford the corresponding racemic flavanones (Scheme 2).



R = OH, OMe, OBr, etc

Scheme 2: Acid and base-catalyzed synthesis of chalcones, racemic flavanones and dihydrochalcones

In 2003, Eddarir successfully synthesized chalcones in acidic condition by using Suzuki coupling synthesis. The activated benzoic acid was coupled with phenylvinylboronic acids in the presence of palladium as a catalyst to give better yield of 80% with less product mixtures. This method was reported to be better than in basic condition with less unwanted side products (Scheme 3).



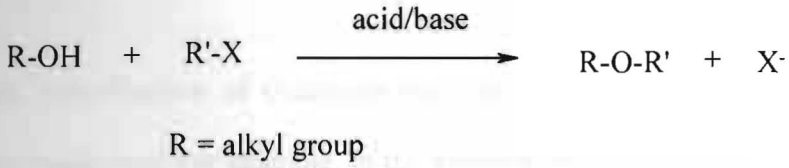
14 **15** **2**

X = Cl, Br etc

Scheme 3 : Chalcones synthesis with activated benzoic acids with phenylvinyl boronic acids

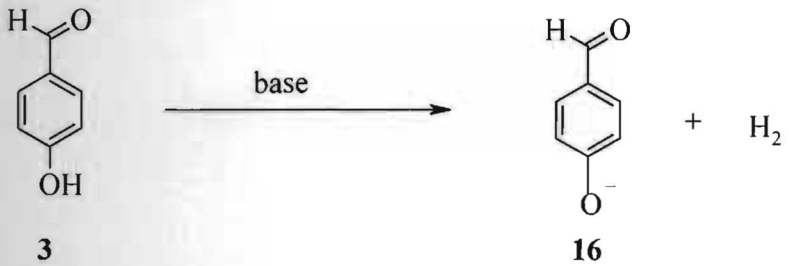
2.2 Etherification

Etherification is a process of attaching alkyl group *via* the hydroxy group (-OH). General etherification reaction can be shown in Scheme 4, where R can be alkyl aromatic compound.



Scheme 4 : General reaction of etherification

In 1997, Wright and his co-workers introduced a simple way to conduct etherification by using H_2SO_4 as a catalyst. The –OH was changed to –OR, in which the R was actually from the alcohol that he used. This method has been done and satisfactory percentage of yield was obtained. However, Wright's method was not feasible to all the phenolic substances. Instead, it was most effective toward acid carboxylic or aliphatic alcohols (Wright *et al.*, 1997;Yeap *et al.*, 2004). This is due to the acidic feature of the phenolic group as the phenol is described to be more acidic than aliphatic alcohols (McMurry, 1992). Due to this problem, some researchers performed etherification on the phenolic group by basic substance such as KOH (Yeap *et al.*, 2004), K_2CO_3 (Ngaini, 2002) and NaH (McMurry, 1992) (Scheme 5).

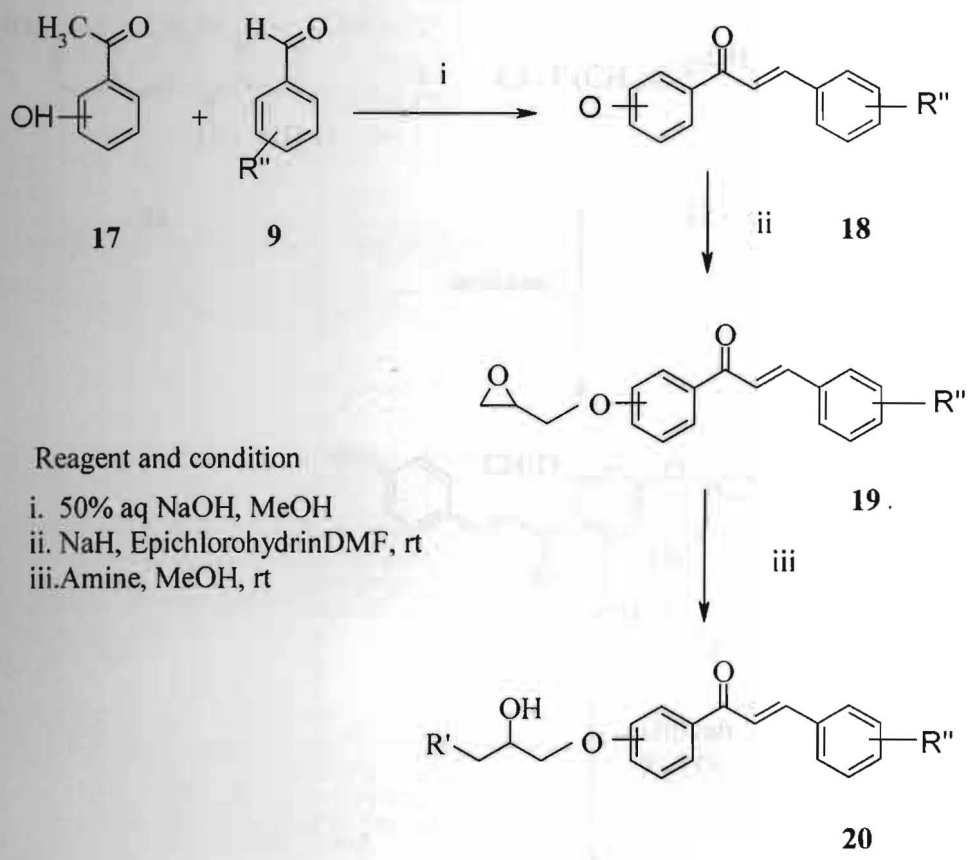


3 **16**

Scheme 5 : Etherification on the phenolic group using NaH as base

Etherification on hydroxychalcones was prepared to produce chalcones derivatives with many purposes. For examples, in the synthesis of chalcones intermediate in pharmaceutical (Valle *et al.*,2005) and also in photochemistry for the preparation of photo-alignment layer (Song *et al.*,2002).

In pharmaceutical, etherification of chalcones was carried out in order to extend the properties of some medicines. For example, in the preparation of aryloxypropanolamines **20** which reported to have antihyperglycemic (blood glucose reluctant properties) (Satyanarayana, 2004) (Scheme 6). The aryloxypropanolamines were first described as $ß_3$-AR agonist by Muller *et al.*, 1986, which is useful for treating diabetes as well as obesity (Goldberg and Frishman, 1995). The chalcones derivatives were prepared using Claisen-Smith condensation. The chalcones obtained were alkylated at hydroxyl groups with *epi*chlorohydrin using NaH as base in dry dimethyl formamide (DMF) at room temperature. The alkylated chalcones **18** were reacted with different amines with aryloxypropeneoxides **19** in methanol at room temperature in order to get aryloxypropanolamines **20**.

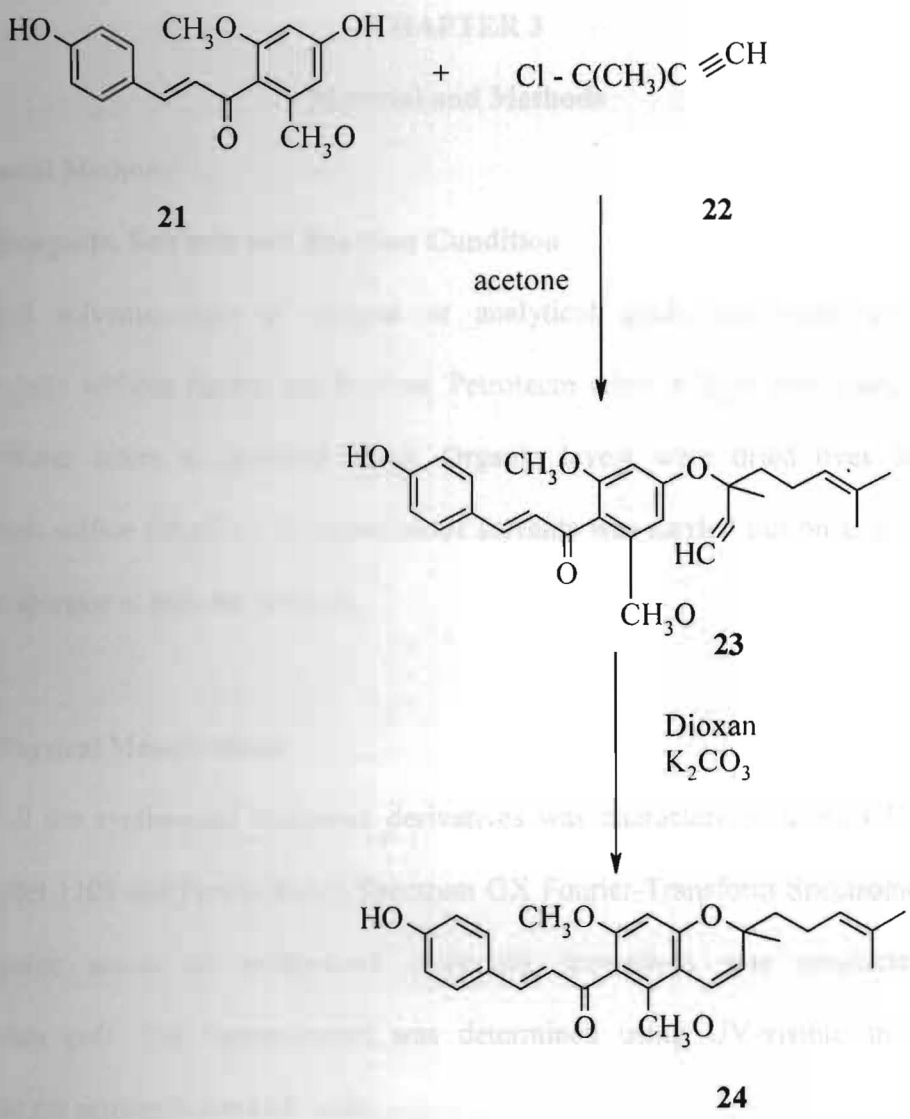


Reagent and condition

i. 50% aq NaOH, MeOH
ii. NaH, EpichlorohydrinDMF, rt
iii.Amine, MeOH, rt

Scheme 6: General synthetic route used to synthesis aryloxypropanolamines

Another example of introducing alkyl group to chalcones derivatives is in the preparation of chromenochalcones (Mathur *et al.*, 1973) (Scheme 7). In this study, etherification on chalcones derivatives was carried out by reacting chalcones **21** with alkylhalide **22** to produce etherified chalcones **23.** Chromenochalcones **24**, was then obtained through the cyclization on side chain of compound **23**. Chromenochalcones can also be naturally produced in the inflorescences of *Flemingia congesta* (Durga, 1981). Both synthetic and naturally chromenochalcones were used successfully for treating tuberculostic and antitubercular activity.



Scheme 7 : General preparation of chromenochalcones

CHAPTER 3

Material and Methods

3.1 General Methods

3.1.1 Reagents, Solvents and Reaction Condition

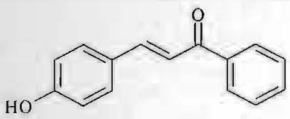
All solvents were of reagent or analytical grade and used as supplied commercially without further purification. Petroleum ether is light petroleum (b.p. 40-60°C). Water refers to dionized water. Organic layers were dried over anhydrous magnesium sulfate ($MgSO_4$). Evaporation of solvents was carried out on a Buchi B490 rotary evaporator at reduced pressure.

3.1.2 Physical Measurement

All the synthesized chalcones derivatives was characterized using CHN Carbo Erba Model 1108 and Perkin Elmer Spectrum GX Fourier-Transform Spectrometer. The bacteriostatic action of synthesized chalcones derivatives was conducted using *Escherichia coli*. The transmittance was determined using UV-visible in order to determine the activity towards *E. coli*.

3.2 Strategy 1

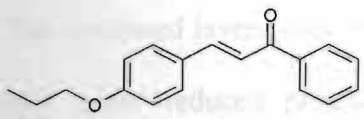
3.2.1 Preparation of (2E)-3-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one, **5**



KOH (62.50g, 0.250 mol) was dissolved in ethanol (200ml, 95%) (solution mixture A). In a separate round bottom flask, acetophenone (30.38 ml, 0.250 mol) was added into 4-hydroxybenzaldehyde (30.53g, 0.250 mol) in ethanol (200 ml, 95%) (solution mixture B).

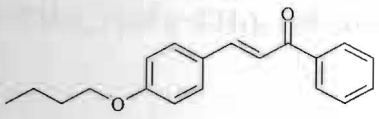
The solution mixture A was added slowly into solution mixture B and stirred overnight at room temperature. The mixture was cooled in ice-bath for 10-15 minutes. Hydrochloric acid (8M) was added into the mixture to form yellow precipitate and filtered. The filtrate was recrystallized from ethanol to give the title compound, 60% as a yellow crystal, m.p. 153-155°C, υ_{max} (KBr/cm^{-1}) 3223 (OH), 3020 (=CH_2), 2848 , 1650 (C=O), 1599 (aromatic)

3.2.2 Preparation of (2E)-3-(4-propoxyphenyl)-3-phenylprop-2-en-1-one, **25**



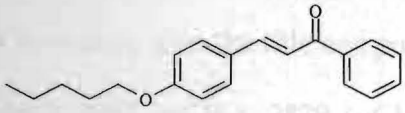
A mixture of (2E)-3-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (4.480g, 0.020 mol), potassium carbonate (4.00g, 0.024 mol), bromopropane (1.82g, 0.020 mol) and tetra-*n*-butyl ammonium (0.74g, 0.002 mol) in MEK (60 ml) was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature filtered. Water (30 ml) was added to the filtrate and layers separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml). The combined layers were washed with water (2 x 20 ml), dried, filtered, and concentrated under reduced pressure. The solid produced was recrystallised from ethanol to give the title compound, 56% yield as a yellow crystal, m.p. 57-58°C, υ_{max} (KBr/cm^{-1}) 2938 (=CH_2), 2880 (−CH_3), 1625 (C=O), 1600 (aromatic)

3.2.3 Preparation of (2E)-3-(4-butoxyphenyl)-3-phenylprop-2-en-1-one, **26**



A mixture of (2E)-3-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (4.48g, 0.020 mol), potassium carbonate (4.00g, 0.024 mol), bromobutane (2.16g, 0.020 mol) and tetra-*n*-butyl ammonium (0.74g, 0.002 mol) in MEK (60 ml) was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature filtered. Water (30 ml) was added to the filtrate and layers separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml). The combined layers were washed with water (2 x 20 ml), dried, filtered, and concentrated under reduced pressure. The solid produced was recrystallised from ethanol to give the title compound, 57% yield as a yellow crystal, m.p. 50-51°C, υ_{max} (KBr/cm^{-1}) 2958 (=CH_2), 2848 (−CH_3), 1652 (C=O), 1589 (aromatic)

3.2.4 Preparation of (2E)-3-(4-pentoxyphenyl)-3-phenylprop-2-en-1-one, **27**

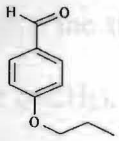


A mixture of (2E)-3-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (4.48g, 0.020 mol), potassium carbonate (4.00g, 0.024 mol), bromopentane (2.48g, 0.020 mol) and tetra-*n*-butyl ammonium (0.74g, 0.002 mol) in MEK (60 ml) was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature filtered. Water (30 ml) was added to the filtrate and layers separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml). The combined layers were washed with water (2 x 20 ml), dried, filtered, and concentrated under reduced pressure. The solid produced was

recrystallised from ethanol to give the title compound, 44% as a yellow crystal, m.p. 63-64°C, υ_{max} (KBr/cm^{-1}) 2942 (=CH_2), 2869 (−CH_3), 1652 (C=O), 1588 (aromatic)

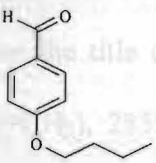
3.3 Strategy 2

3.3.1 Preparation of 4-propoxybenzaldehyde, **28**



A mixture of 4-hydroxybenzaldehyde (2.44g, 0.020 mol), potassium carbonate (4.00g, 0.024 mol), bromopropane (1.82g, 0.020 mol) and tetra-*n*-butyl ammonium (0.74g, 0.002 mol) in MEK (60 ml) was heated at reflux for 12 hours. The reaction mixture was cooled to room temperature filtered. Water (30 ml) was added to the filtrate and layers separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml). The combined layers were washed with water (2 x 20 ml), dried, filtered, and concentrated under reduced pressure. The crude oil was purified in flash column using petroleum ether and acetyl acetate in the ratio 1:10 as a solvent to give the title compound, 67% yield as a viscous brown oil, υ_{max} (Thin film/cm^{-1}) 2967 (=CH_2), 2879 (−CH_3), 1688 (CHO Aldehyde), 1600 (aromatic)

3.3.2 Preparation of 4-butoxybenzaldehyde, **29**



A mixture of 4-hydroxybenzaldehyde (2.44g, 0.020 mol), potassium carbonate (4.00g, 0.024 mol), bromobutane (2.16g, 0.020 mol) and tetra-*n*-butyl ammonium (0.74g, 0.002